(iii) said chitosan powder has a mean particle size diameter in the range of about 0.5 microns to about 400 microns.

Although the Applicant has argued the nonobviousness of the claimed invention over the cited references and supported the nonobviousness of the invention by the showings of Dr. Shimono's Declaration executed on July 25, 2006 and Dr. Shimono's Supplemental Declaration executed on April 12, 2007, the Examiner still adheres to his position. The Applicant respectfully disagrees with the Examiner's position.

Thus, the Applicant traverses the patentability rejection of the claimed invention along the USPTO's Guideline issued on October 2007, that is, by firstly pointing out the Examiner's error in the Graham factual findings, and secondly, by pointing out the Examiner's misunderstanding of unexpected results of the claimed invention.

I. Examiner's error in the Graham factual findings

(i) The Examiner points out in the Action that "The claims recite a range from 1:4-4:1, where the claims exemplify a radio from 1:1-3:7. However, the 3:7 ratio is encompassed within the wider range of the claimed ratio." (cf. the Office Action, page 3, Item 6, lines 2-4)

However, the Applicant cannot understand what is meant by these sentences.

Further, in the examples of the present invention, preparations having the ratios of 2:1, 1:1 and 1:2 are exemplified. See Examples 3-5 on pages 19-20 of the specification.

Further, in Dr. Shimono's Declaration executed on July 25, 2006 and Supplemental Declaration executed on April 12, 2007, other preparations having the ratios of 4:1, 2:1, 1:1, 1:2 and 1:4 are exemplified. These preparations are all inclusive within the range of the claimed ratio.

As experimentally proved and shown in Dr. Shimono's Declaration and Supplemental Declaration, the preparations having the specific ratio as defined in claims 29 and 33 of the present invention have superior effects. It seems to the Applicant that the Examiner did not well understand the distinction from the cited references though the Applicant has explained it by

referring to the comparative experimental results shown in Dr. Shimono's Supplemental Declaration. The cited references do not teach or even suggest such superior effects. It shall be noted that Lerner et al. '332 do not disclose the specific ratio of 1:1-3:7.

(ii) The Examiner further points out that "The process of the '332 patent provides sustained release (Figures) of a coated solid dosage form." (cf. the Office Action, page 3, Item 6, lines 5-6)

However, this understanding is wrong. The Lerner et al. '332 patent does never disclose that their preparation is a sustained-release preparation. Even the term "sustained" is never mentioned in Lerner et al. On the contrary, the invention of Lerner et al. is directed to "a delivery system for targeted delivery to specific locations in the alimentary canal" (cf. Lerner et al. '332 patent, col. 6, lines 2-4). And it is disclosed that "the location of drug release is controlled by varying specific parameters such as ..." (cf. Lerner et al. '332 patent, col. 6, lines 31-36). Thus, the invention of Lerner et al. is directed not to sustained release of a drug, but rather is directed to release of a drug at a specific location of the digestive tract.

Even from the Figures of Lerner et al., it is not taught that the release of drug is owing to a sustained release. All dissolution tests carried out by Lerner et al., the results of which are depicted in the Figures, were tests carried out with a formulation of an intestinal fluid TS based upon USP XXII. (cf. Lerner et al, '332, col. 15, lines 47 et seq.) Such intestinal fluid only corresponds to the 2nd fluid used in Dr. Shimono's Declaration and Supplemental Declaration. Such intestinal fluid is markedly different from the 1st fluid (artificial gastric juice) used in Dr. Shimono's Declaration and Supplemental Declaration. Therefore the experiments described in Lerner et al. fail to demonstrate a sustained release of drug under hypothetical oral administration conditions in comparison to the experiments conducted by the Applicant using preparations of the claimed invention.

Accordingly, the Examiner's indication that Lerner et al. relates to a "sustained release (Figures)" is clearly wrong. Further, the Examiner's indication that "the resulting products are

within the same field of endeavor and solved the same problem." (cf. Office Action, page 3, lines 3-2 from bottom) is clearly wrong.

(iii) The Examiner points out further that the Lerner et al. reference is silent to the specific particle size of the chitosan powder, but the Examiner takes the position that chitosan powder is a common ingredient in coating materials as is known in the art as seen in Dutkiewicz et al '322 which discloses a chitosan coating suspension comprising chitosan particles ranging in size from 0.1-80 microns, and the powder suspension is applied to hydrophobic and/or hydrophilic polymers. (cf. Office Action, page 4, Item 7).

Based on this presumption, the Examiner indicates that it would be easy to apply the chitosan suspension to the method of Lerner et al. invention.

However, this position of the Examiner is incorrect. Although Dutkiewicz et al '322 discloses that "When the chitosan material is not soluble in the solvent, it can be made as a suspension for coating." (cf. '322 patent, col. 3, lines 27-28), it is not disclosed how to prepare the suspension and how to use it. Rather, in Dutkiewicz et al '322, the only concrete disclosure about how chitosan is used is by first suspending it in water and then dissolving it homogeneously by adding an acid, and then it is used for coating in the form of a homogenous solution (cf. '322 patent, col. 4, lines, 51, 55, etc., and col. 5, line 64 to col. 6, line 8).

Thus in the solution of chitosan in the Dutkiewicz et al. '322 patent, the chitosan is not present in particle form and hence has no particle size. Accordingly, it will be impossible to combine the teachings of Lerner et al. with Dutkiewicz et al. since Lerner et al. teaches using chitosan powder while Dutkiewicz et al. teaches making a dissolved chitosan solution. Further, it will be impossible to understand the correlation of the particle size of chitosan powder and antimicrobial activity of Dutkiewicz et al.

Moreover, the invention of Dutkiewicz et al '322 is concerned with a technique of enhancing antimicrobial activity by coating with chitosan solution in a material such as a polypropylene nonwoven fibric which is useful for certain components of personal care articles (e.g. diaper liners) (cf. '322 patent, ABSTRACT, col. 1, lines 15-18, etc.). Thus, the technique of

Dutkiewicz et al '322 is substantially different from the pharmaceutical preparation of the present invention.

In summary, one skilled in the art would not have been motivated to combine the teachings of Lerner et al. and Dutkiewicz et al. as argued by the Examiner.

II. Misunderstanding of unexpected results of the present invention

Furthermore, the Examiner has overlooked or misunderstood the unexpected results of the present invention which were experimentally proved by Dr. Shimono's Declaration and Supplemental Declaration.

(i) The Examiner points out that "such modulations in ratio (1:4 to 4:1) are merely an optimization of ranges." (cf. Office Action, page 3, Item 6, lines 4-5)

However, this understanding of the Examiner is wrong.

Firstly, the present invention is concerned with a sustained release pharmaceutical preparation, and the excellent sustained release properties of the present preparation have been experimentally proved as shown in Dr. Shimono's Declaration and Supplemental Declaration.

The superior sustained release properties of the present preparations have been proved with respect to the preparations prepared with every claimed polymer. It was also experimentally proved that all of the preparations disclosed in all Examples in the cited Lerner et al. '332 patent showed no sustained release property by the Applicant's tests. That is, the Reference Preparations of the Declarations according to the teachings of Lerner et al. dissolved (decomposed) immediately.

Thus, any person skilled in the art could never have predicted the superior sustained release properties of the claimed preparations from the cited Lerner et al '332 patent.

(ii) The Examiner further points out that "the resulting products are within the same field of endeavor and solve the same problem." (cf. Office Action, page 3, Item 6, lines 6-7)

However, as mentioned above, the invention of Lerner et al. is directed at release of a drug at a specific location, and the problem to be solved is entirely different from the present invention.

The Examiner is kindly requested to remember that at the interview on December 13, 2006 with the undersigned representative, the Examiner suggested reciting the term "sustained-release" in the claims of the present invention in order to distinguish the claimed invention from the "Burst-type" preparation of Lerner et al. '322. The pending claims incorporate the Examiner's suggestion.

(iii) The Examiner further points out as "it would have been obvious to combine the chitosan suspension of the '322 patent into the coating composition of the '332 patent in order to provide an even coating and improve the release of the active agent in the core. (cf. Office Action, page 4, Item 8)

However, the Examiner's understanding is clearly wrong in the light of the experimental results of Dr. Shimono's Declaration, wherein comparative experiments have been conducted by varying the particle size of the chitosan suspentions as mentioned in Dutkiewicz et al. '322.

Dutkiewicz et al. '322 discloses the particle size but it is simply mentioned as a particle diameter of from about 0.1 to about 80 microns" without any specific example nor any experiment of the effects of varying the particle size.

Further, as mentioned above, in Dutkiewicz et al. '322, chitosan is used in the form of a solution wherein the particle size of chitosan is no longer relevant to the properties of the coating.

The chitosan solution used in Dutkiewicz et al. '322 is prepared by a conventional method, i.e. suspending chitosan in water and adding an acid thereto (e.g. acetic acid, hydrochloric acid) to dissolve chitosan to give a solution of chitosan.

The suspension of chitosan powder used in the present invention is entirely different from such chitosan solution.

In the present invention, the product of the present invention has a first layer of the coating wherein chitosan particles are dispersed having a mean particle size diameter of 0.5 microns to 400 microns. The superior sustained release properties of such products of the present invention have been experimentally proved as shown in Dr. Shimono's Declaration and Supplemental Declaration. It shall also be noted that the large microns of the chitosan particles of the present invention are not included within the range disclosed in Dutkiewicz et al. '322.

Accordingly, in view of the experimental results as shown in Dr. Shimono's Declaration and Supplemental Declaration, no person skilled in the art could have predicted the superior effects of sustained release properties (in the wide area of the digestive tract) of the preparations having the first coating layer of chitosan powder of the specified particle sizes even from a combination of the teachings of Lerner et al. '332 and Dutkiewicz et al. '322.

The Examiner is also kindly requested to remember that at the interview on December 13, 2006, the Examiner suggested to recite the "particle size of chitosan" to the claims of the present invention in order to distinguish from the preparation of Lerner et al. '322. The pending claims incorporate the Examiner's suggestion.

III. Examiner's indications in the past Office Actions

The Examiner has indicated various things from the Office Action dated June 17, 2005 until the outstanding Office Action, and the Applicant has responded sincerely and earnestly to those Office Actions, as summarized below.

(i) Office Action dated June 17, 2005

The Applicant responded thereto by amending the claims so as to clarify the characteristics of the invention and explained in detail the differences of the present invention from the cited Lerner et al '332. As the result, the rejection under 35 USC §102 was withdrawn.

(ii) Final Office Action dated January 31, 2006

The Applicant (through its attorney) had an interview with the Examiner on April 11, 2006 and then it was suggested by the Examiner to show some comparative experiments. Along with the Examiner's suggestion, the Applicant submitted some comparative experiments in comparison with the preparations of Lerner et al. '332. The response with Dr. Shimono's Declaration including the comparative experiments as well as an Amendment to the claims were submitted together with an RCE.

(iii) Office Action dated October 16, 2006

The Applicant (through its attorney) had another interview with the Examiner on December 13, 2006, and then it was suggested by the Examiner to show some additional comparative experiments. Along with the Examiner's suggestion, the Applicant submitted Dr. Shimono's Supplemental Declaration setting forth some additional comparative experiments to compare the preparations of Lerner et al '332 in other ratios of the components and other kinds of polymer and with varying the coating thickness and particle sizes of chitosan.

(iv) Office Action dated July 12, 2007

The Applicant responded by amending the claims wherein the particle size of chitosan powder was specified together with an RCE.

(v) Outstanding Office Action dated February 7, 2008

The instant response is now responding thereto in the line as mentioned herein.

As briefly mentioned above, the Applicants have sincerely and earnestly responded to each Office Action. That is, the Examiner pointed out in these Office Actions that the Lerner et al. '332 teach the importance of five factors of (1) particle size, (2) coating thickness, (3) kinds of material (particle), (4) ratio of the components, (5) kinds of polymer, and then he suggested to study the parameters of these factors.

Along with the Examiner's suggestion, the Applicant carried out various comparative experiments taking into consideration the parameters of the above (1) to (5) factors, and as a result, the Applicant obtained submitted the results in two Rule 132 Declarations, showing the superior properties of the preparations of the present invention in comparison with the preparations of Lerner et al '332. Then the Applicant argued the unobviousness of the present invention over the cited reference based on the experimental results.

Despite the sincere and earnest responses of the Applicant, the Examiner does not fully take into consideration the situation and the responses of the Applicant to past Office Actions, and he again rejects the present invention under 35 USC §103 as being obvious over the Lerner et al. '332 in combination with Dutkiewicz et al. '322 (which has little relationship with the present invention).

The Applicant wishes to ask the Examiner to consider carefully the arguments and experimental results showing the superior sustained release property of the present invention (which are entirely different from the effects taught and/or suggested by the cited references) which have been submitted in its responses to Office Actions in the past in addition to the above-mentioned argument.

IV. Summary of Dr. Shimono's First Declaration

For the Examiner's convenience, a copy of Dr. Shimono's First Declaration is attached hereto.

Points to note are as follows:

As seen from the Declaration, based upon the suggestion by the Examiner, the preparations of Examples 3, 4, 5, 7 and 8 of the cited Lerner et al. reference were submitted to the comparative experiments with the inventive preparations. The Lerner et al. preparations are referred to as "Reference Preparations A-E". The preparations of this invention are referred to as "Preparations F-L". As the preparations of the present invention, those having various ratios of the chitosan to the water-insoluble polymer (Eudragit RS) of from 1:4 to 4:1 were tested.

(1) In Experiment 1, the release of the active ingredient was compared by using a 1st fluid as defined in Japanese Pharmacopeia (which is artificial gastric juice).

As is shown in Fig. 1, in the preparations of the cited Lerner et al., the active ingredient released almost within one hour, but on the other hand, the preparation of the present invention released the active ingredient only about 20% even after two hours.

Accordingly, it is clear that the preparations of the cited Lerner et al. released the active ingredient mostly in the stomach, but the preparation of the present invention shows excellent sustained release properties and can release the ingredient after passing the stomach. Thus, the preparation of the present invention is significantly distinguished from the preparation disclosed in the cited Lerner et al., and hence the present invention would have never been suggested by the cited Lerner et al. reference.

(2) In Experiment 2, the comparison was carried out for observing the release of active ingredient in a hypothetical oral administration by using the 1st fluid (artificial gastric juice), a 2nd fluid (artificial intestinal fluid) and an aqueous solution of pH 4.0 (hypothetical fluid in the large intestine).

As seen from the experimental results, the preparation (Ref. Prepar. C) of the cited Lerner et al. swelled and disintegrated merely by the treatment with the 1st fluid (and hence could not be subjected to the test with other dissolution media) and released 60% or more of the active ingredient within 2 hours. On the other hand, the preparation (Prepar. G) of the present invention could release the active ingredient gradually through the treatment with the 1st fluid, the 2nd fluid and the solution of pH 4.0 and hence can show the desired sustained release properties.

It is apparent from this comparison that the difference between the preparation of the

cited Lerner et al. and that of the present invention is solely in the kind of the dispersed particles, calcium pectinate (in Lerner et al.) or chitosan (in the present invention). While both preparations used a common water-insoluble polymer (i.e. Eudragit RS), nevertheless, both preparations showed significant difference in the release of the active ingredient.

This means that the preparation of the present invention using chitosan as the dispersed particles can give unexpectedly superior sustained release properties, which would have never been predicted from the cited Lerner et al.

(3) In Experiment 3, the preparations of the present invention, those having various ratios of the chitosan to the water-insoluble polymer (Eudragit RS) of from 1:4 to 4:1 were tested.

As is clear from Fig. 3, the preparations of the present invention could show the excellent sustained release properties for a long time (more than 8 hours) in the ratio of the chitosan and the water-insoluble polymer (Eudragit RS) within the ratios of 1:4 to 4:1.

(4) In Experiment 4, the pellet preparations of the present invention were subjected to the experiment in a hypothetical oral administration by using the 1st fluid (artificial gastric juice), the 2nd fluid (artificial intestinal fluid) and an aqueous solution of pH 4.0 (hypothetical fluid in the large intestine) like in Experiment 2. One of the preparations tested was an enteric coating preparation (Prepar. L).

As is seen from Fig. 4, Prepar. K of the present invention released partly the active ingredient by treating with the 1st fluid, because chitosan dissolved partly with the 1st fluid, and showed sustained release of the active ingredient by treating with the 2nd fluid (because chitosan is not dissolved at a neutral pH and hence the preparation can keep the sustained release of the active ingredient).

The enteric coating preparation (Prepar. L) did not release the active ingredient with the 1st fluid (artificial gastric juice) due to the enteric coating and did not release the ingredient either with the 2nd fluid (artificial intestinal fluid) because chitosan does not dissolve at a neutral pH range and then immediately released the active ingredient with the solution of pH 4.0 because the pellet was somewhat swelled by the treatment with the 2nd fluid and then chitosan is dissolved

with an acidic solution (pH 4.0).

(5) In Experiment 5, the pellet preparations (Prepar. K and Prepar. L) of the present invention were subjected to *in vivo* test in rats, wherein the blood concentration of the active ingredient was measured.

As is seen from Fig. 5 these pellet preparation showed similar release behavior to that in Experiment 4 (*in vitro* test).

That is, Prepar. K showed sustained release properties over 12 hours and also released when passing through the stomach (during first 2 hours). On the other hand, the enteric coating preparation (Prepar. L), which is a colonic delivery preparation as claimed in original claim 1 (= new claim 22), did not release the active ingredient during passing though the stomach (first 2 hours) but after reaching the large intestine (after 5 hours), the active ingredient was rapidly released, because chitosan was decomposed faster with the bacteria in the large intestine in addition to the dissolution with an acidic solution.

As is clear from the above experimental results, the preparation of the present invention using chitosan as the dispersed particles show significantly distinguishable release properties. Such excellent properties would have never been predicted from the cited Lerner et al. reference.

Dr. Shimono summarized his opinions about the comparative experiments at the end of the first Declaration. Specifically, he stated that:

"It is my opinion based upon my knowledge and experience in this field:

(1) that the reference preparations disclosed in the cited Lerner et al. reference released the active ingredient very rapidly by the treatment with 1st fluid (artificial gastric juice), which means that it is difficult to control the rapid release of the active ingredient in the stomach and hence is not suitable for sustained release preparation; on the other hand, the preparations of the present invention using chitosan as the main component in the coating layer can give the desired sustained release of the active ingredient from the stomach to the large intestine with keeping the original shapes of tablets/pellets without swelling or disintegration, that is, the preparations of the present invention could show continuous release of the active ingredient by the treatment with 1st fluid (pH 1.2, for 2 hours), 2nd fluid (pH 6.8, for 3 hours) and an acidic aqueous solution (pH

4.0, for 3 hours) which is simulated to the conditions (pH value and time of passing through) in the digestive tract in biobody;

(2) that the preparations disclosed in the cited Lerner et al. reference are rapidly disintegrated by the treatment with 1st fluid (artificial gastric juice), and hence it is assumed that these preparations will be rapidly disintegrated when administered orally, and hence, it will be unable to give sustained release property to these preparations of the Lerner et al. reference, in other words, these preparations of Lerner et al. will be not able to tolerate the shear which will be loaded within the stomach;

(3) that it would never been predicted from the cited Lerner et al. reference that the release of active ingredient within the stomach can be controlled by using chitosan coating like in the present invention, because it is not expected to improve such a release of active ingredient in the stomach by suspending dispersed particles in a water-insoluble polymer for the coating medium as specifically disclosed in the cited Lerner et al. reference;

(4) that as is seen from Experiment 2, under the conditions simulated to the case of oral administration, i.e. by treating with 1st fluid (artificial gastric juice, pH 1.2, for 2 hours), 2nd fluid (artificial intestinal fluid, pH 6.8, for 3 hours) and an acidic aqueous solution simulated to the conditions in large intestinal, pH 4.0, for 3 hours), the preparation of Lerner et al. reference (Ref. Prepar. C) and the preparation as claimed in claim 7 of the present invention (Prepar. G) showed significantly different dissolution profile, and from this viewpoint, the present invention would never been predictable from the cited Lerner et al. reference; and

(5) that as is seen from Experiment 4, the enteric coating colonic delivery preparation of the present invention can keep the original shape of preparation (tablets and pellets) even by treating with 1st fluid (pH 1.2, for 2 hours) and 2nd fluid (pH 6.8, for 3 hours), that is, can keep the original shape with releasing the active ingredient in very small amount (i.e. substantially no release of the active ingredient) for about 5 hours after administration and when reached to around the large intestine (after about 4-5 hours) the blood concentration of the active ingredient is increasing, and hence, by applying an enteric coating to the preparation as claimed in claim 7, the resulting enteric coating preparation of the present invention is suitable as a colonic delivery

preparation, which would never been predicted from the disclosure of the cited Lerner et al. reference."

V. Summary of Dr. Shimono's Supplemental Declaration

For the Examiner's convenience, a copy of Dr. Shimono's Supplemental Declaration is attached hereto.

Points to note are as follows:

(1) The Examiner suggested that the Applicant submit additional comparative experiments adding Ref. Preparation A, B, C, D and E at a:b of 3:7 and a:b of 1:1.

Based upon the Examiner's suggestion 1, Ref. preparations A, D and E at a:b of 3:7 and a:b of 1:1 were prepared along with the formulations disclosed in Examples 3, 7 and 8 of Lerner et al. as Ref. prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1), and E(3/7) and were compared with the Prepar. F, G, H, I, and J of the present invention (cf. Experiment 1A in Dr. Shimono's Supplemental Declaration).

Reference preparations (a:b = 1:1 or 3:7) corresponding to Ref. preparations B and C were not prepared, because Ref. preparations B and C are common to Ref. preparation A in the kind of the dispersed particles (calcium pectinate). Further it will be well assumed that those preparations will show the same or similar release profile in the light of the experimental results shown in Experiment 2A, wherein the release profile of the preparations were substantially not affected by the kinds of the water-insoluble polymers (even by using ethyl cellulose or Eudragit NE30D® instead of Eudragit RS®).

As the Examiner will see from said comparative experimental data, even when the ratio of (a):(b) was changed to 1:1 or 3:7, the preparations of Lerner et al. showed very rapid dissolution profile as the reference preparations A, B, C, D and F having the ratio of (a):(b) of 7:3. It is assumed that in the Ref. preparations, the tablets would be swollen with the 1st fluid and then disintegrated, by which the active ingredient was dissolved out very rapidly. On the other hand, in Prepar. F, G, H, I and J of the present invention with the claimed ratio of (a):(b) of

1:4 to 4:1, the coating of the tablets would not be swollen and the original tablet form was kept for more than 8 hours, and thereby the active ingredient was dissolved out very gradually and can show excellent sustained release properties.

(2) The Examiner suggested that the Applicant submit additional comparative experiments adding Prepar. F, G, H, I, J, K and L using b: ethyl cellulose and b: Eudragit NE30D.

Based upon the Examiner's suggestion, the preparations of the present invention using b: ethyl cellulose and b:Eudragit NE30D® were prepared as Prepar. M, N and Prepar. O of the present invention and the release properties of the active ingredient were tested likewise (cf. Experiment 2A and Experiment 3A in Dr. Shimono's Supplemental Declaration).

As the Examiner will see from these experimental data, the Prepar. M and N and Prepar. O of the present invention using ethyl cellulose and Eudragit NE30D® as the water-insoluble polymer showed excellent sustained release properties as like as the Prepar. F, G, H, I and J of the present invention using other water-insoluble polymer, Eudragit RS® (cf. the Fig. 1A in Mr. Shimono's Supplemental Declaration as well as Fig. 1 to Fig. 3 in Dr. Shimono's former Declaration).

Thus, it has experimentally been proved that the preparations of the present invention can show the excellent sustained release properties in all cases using as the water-insoluble polymer Eudragit RS®, ethyl cellulose and Eudragit NE30D®.

(3) The Examiner tentatively suggested to specify the thickness of the coating in the comparative examples in the Examiner's suggestion 3. For all of the Ref. preparations of Lerner et. al. as well as preparations of the present invention experimented in this time the thickness of the coating was specified as shown in Fig. 1A, Fig. 2A and Fig. 3A of Dr. Shimono's Supplemental Declaration, wherein the thickness of the coating layer of the preparations is shown in the parenthesis after each preparation.

As seen from Fig. 1A, although Ref. Prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1),E(3/7) of Lerner et al. had a larger coating thickness of from 139 to 107 μm than that (100 μm) of the preparations of the present invention, the Ref. preparations of Lerner et al. dissolved more

rapidly. This suggests that the dissolution profile of the preparations was almost not effected by thickness of the coating layer, but was effected much more by the kinds of the dispersed particles in the coating layer.

Lerner et al. mention as "Drug release is controlled by varying the following parameters; (1) size of the particulate matter; (2) thickness of the coating; (3) type of material forming the particulate matter; (4) ratio of particulate matter; and (5) water-insoluble film forming material." (cf. Lerner et al. USP 5,840,332, Col. 11, lines 51-55). However it has been found that as far as concerning at least the preparations of the present invention, among the above parameters, the parameter (3) type of material forming the particulate matter was the most important while other parameters such as (1) size of the particulate matter (the dispersed particle), (2) thickness of the coating film, (4) the ratio of the particulate matter, and (5) the kinds of the water-insoluble polymer were not such important parameters. It has been found by the present inventors that by coating a medicament-containing material with a coating solution wherein chitosan is dispersed in a water-insoluble polymer selected from Eudragit RS®, ethyl cellulose and Eudragit NE30D®, the preparations showed unexpectedly superior sustained release properties of the active medicament contained in the preparation when orally administered.

According to common knowledge in the field of pharmaceuticals, it may be generally said that "the thinner the coating in a medicament, the quicker the release of the active ingredient from the core material." Nevertheless, it is not necessarily correct regarding the preparation of the present invention with coating of the dispersed solution wherein chitosan powder is dispersed in a solution of a water-insoluble polymer, which was proved experimentally as mentioned above.

Thus, even from this viewpoint only, the present invention could have never been expected from the cited Lerner et al. reference.

(4) The Examiner further tentatively suggested to specify the chitosan particle size in the comparative examples. In Experiment 2A, the preparations having different particle sizes of chitosan were compared. That is, in Prepar. M and Prepar. N, the chitosan powder to be dispersed in the water-insoluble polymer was the pulverized one (particle size, 6 μm) and the

unpulverized one (particle size, 110 μm), respectively, and further both preparations had different thickness of the coating, i.e. 192 μm (Prepar. M) and 166 μm (Prepar. N). However, as is seen from the experimental results shown in Fig. 2A, the excellent release profiles were similar to each other.

Thus, it has been experimentally proved that the excellent sustained release properties of the preparations of the present invention are not substantially affected by the chitosan particle size or by the thickness of the coating.

As is clear from the above explanation based on the comparative experiments shown in Dr. Shimono's Supplemental Declaration as well as his former Declaration, the preparation of the present invention comprising a medicament-containing solid material and a water-insoluble coating film, wherein said coating film consisting essentially of a water-insoluble polymer selected from ethyl cellulose, Eudragit RS® and Eudragit NE30D® and a chitosan powder dispersed in said polymer, has superior release profile (sustained release properties) of the active ingredient contained in the medicament-containing solid material (core). Such excellent sustained release properties of the present preparation are not taught or suggested by the cited Lerner et al. reference.

Dr. Shimono summarized his opinions about the comparative experiments at the end of the Supplemental Declaration. Specifically, he stated that:

" It is my opinion based upon my knowledge and experience in this field:

(1) that in the reference preparations disclosed in the cited Lerner et al. reference, even when the ratio of the dispersed particles (a) and the water-insoluble polymer (b) of the coating film was varied to 1:1 and 3:7, the reference preparations of Lerner et al. released the active ingredient very rapidly by the treatment with 1st fluid (artificial gastric juice) as like as the reference preparations having the ratio of (a):(b) of 7:3 as shown in my former Declaration, and further even when the thickness of the coating film on the core was made larger (e.g. 193 - 107 pm) than that (100 pm) of the preparations of the present invention, the dissolution properties were

not changed, which means that according to the preparations of the cited Lerner et al., it is difficult to control the rapid release of the active ingredient in the stomach and hence is not suitable for sustained release preparation;

(2) on the other hand, the preparations of the present invention using chitosan as the dispersed particles in the coating layer could give the desired sustained release of the active ingredient from the stomach to the large intestine with keeping the original shapes of tablets/pellets without swelling or disintegration, even though the ratio of the dispersed particles (a) and the water-insoluble polymer (b) of the coating film was varied, and further the kind of the water-insoluble polymer was changed to ethyl cellulose or Eudragit NE30De from Eudragit RSe used in Prepar. F, G, H, I and J, the excellent sustained release properties were not affected,

(3) as seen from Experiments 2 and 4 in my former Declaration, the preparations of the present invention in various embodiments as defined in claims could show continuous release of the active ingredient by the treatment with 1st fluid (pH 1.2, for 2 hours), 2nd fluid (pH 6.8, for 3 hours) and the weak acidic aqueous solution (pH 4.0, for 3 hours) which are simulated to the conditions (pH value and time of passing through) in the digestive tract in biobody; and

(4) further the enteric coating colonic delivery preparation of the present invention can keep the original shape of preparation (tablets and pellets) even by treating with 1st fluid (pH 1.2, for 2 hours) and 2nd fluid (pH 6.8, for 3 hours), that is, for about 5 hours after administration and until reaching to around the large intestine, and when reached to around the large intestine (after about 4-5 hours), the blood concentration of the active ingredient increases, and hence, such an enteric coating preparation of the present invention is suitable as a colonic delivery preparation, which would never been predicted from the disclosure of the cited Lerner et al. reference;

(5) as is seen from Experiment 1A (Fig. 1A), although Ref. prepar. A(1/ 1), A(3/7), D(1/ 1), D(3/7), E(1/ 1), E(3/7) of Lerner et al. had a larger coating thickness of from 139 to 107pm than that (100 pm) of the preparations of the present invention, the Ref. preparations of Lerner et al. dissolved more rapidly, which suggests that the dissolution profile of the preparations was almost not affected by thickness of the coating layer, but was affected much more by the kinds of the dispersed particles in the coating layer; and further as is seen from Experiment 2A (Fig. 2A),

although the preparations had different particle size of chitosan, that is, the pulverized one (particle size, 6 pm) in Prepar. M and the unpulverized one (particle size, 110 pm) in Prepar. N, and further had different thickness of the coating, i.e. 192 pm (Prepar. M) and 166 pm (Prepar. N), the excellent release profiles were similar to each other, which proved that the excellent sustained release properties of the preparations of the present invention are not substantially affected by the chitosan particle size or by the thickness of the coating; and

(6) Lerner et al. mention as "Drug release is controlled by varying the following parameters; (1) size of the particulate matter; (2) thickness of the coating; (3) type of material forming the particulate matter; (4) ratio of particulate matter; and (5) water-insoluble film forming material." (cf. Lerner et al. USPN 5,840,332, Col. 11, lines 51-55), but it has been found that among the above parameters the item (3) type of material forming the particulate matter was the most important while other parameters such as (1) size of the particulate matter (the dispersed particle), (2) thickness of the coating film, (4) the ratio of the particulate matter, and (5) the kinds of the water-insoluble polymer were not so important parameters, and it would have never been predicted from the cited Lerner et al. reference that the preparations of the present invention using chitosan as the dispersed particles (the particulate matter in Lerner et al.) give such excellent sustained release properties.

Thus, it is respectfully submitted that the patentability of the present invention over the cited Lerner et al. reference is clear from the above explanation based on the comparative experiments. In view of the foregoing, it is respectfully submitted that the Rule 132 Declarations of record do demonstrate the unexpected properties of the claimed invention over the prior art and the experimental evidence is commensurate in scope with the claimed invention.

Favorable reconsideration and allowance is now kindly solicited.

Respectfully submitted,

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